example, at pages 8, lines 9-14 of the specification and in Examples 4-6. No new matter is added.

It is submitted that these amendments place the application in condition for allowance, and thus are appropriate to be made pursuant to 37 C.F.R. § 1.116.

1. Section 102(b).

Claims 31, 32, 34, 35 and 37 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Gutniak et al., N. Eng. J. Med. 326:1316-1322 (1992). The Examiner suggests that:

> Gutniak et al., teaches pharmaceutical compositions comprising GLP 1 (7-36) amide (see page 1317-1318, in particular).
>
> . . .
>
> Applicant argues that the preamble in a claim carries patentable weight when it defines the claim, citing Bell Communications Research, Inc. v. Vitalink Communications Corp. 34 USPQ2d 1816 (Fed Cir. 1995). However, as applicant has stated in summarizing the decision, the claims under discussion were method claims, not product claims, as is the case in a composition claim. In a product claim if the prior art teaches all of the components of the claim the intended use for the product has no patentable weight.

March 31, 1998 Office Action at page 2.

Applicant disagrees with the Examiner's characterization of the applicable law. In determining that a language in a preamble limits the invention as a whole, there is no distinction made between product claims and method claims. For example, the preamble has been held to limit the scope of product claims in Kropie v. Robie, 88 USPQ 478 (CCPA 1951) (the term "abrasive article" in a count is essential to point out the

invention, and distinguishes the count from an earlier application disclosing a resin recited in the body of the count); In re Bulloch, 203 USPQ 171 (CCPA 1979) (there was little doubt that the applicants intended to limit the claims containing a preamble, "stable color developer concentrate" to color developer concentrates of alcoholates of AEMP orthophosphates). Thus, the language in a preamble, such as the presently pending claims 31-37, a pharmaceutical composition "for the treatment of Type I diabetes mellitus," is properly interpreted as limiting the scope of claim 31 and its dependent claims 32, 34, 35 and 37. One of ordinary skill in the art would have had no motivation to prepare a pharmaceutical composition for the treatment of Type I diabetes.

Nevertheless, with traverse and solely to advance prosecution of this application, and expressly preserving the opportunity to file a continuing application directed to the subject matter of these claims, applicant cancels claims 31-37 in this Response.

2. Section 103.

Claims 15-19, 23-27, 33 and 36 stand rejected under 35 U.S.C. § 103 as allegedly unpatentable over in view of Gutniak et al., N. Eng. J. Med. 326:1316-1322 (1992), in view of U.S. Patent No. 5,424,286 and D'Alessio et al., J. Clin Invest. 93:2263-2266 (1994). The Examiner states:

> Applicant's arguments filed 12-29-97 have been fully considered but are not found persuasive.
>
> Applicant argues that the '286 patent mischaracterizes the Gutniak et al., article. However, the '286 patent

> draws conclusions based upon experimental data taught by Gutniak et al. Furthermore, another skilled artisan, D'Alessio recognized the importance of Gutniak's et al., article when they summarized Gutniak's work in their introduction. It is well established that Type I diabetics do not produce enough insulin in response to a meal. Since Gutniak et al., teaches that GLP-1(7-36)amide decreases the need for external insulin in Type I diabetics after a meal, it would be obvious to treat Type I diabetics with the peptide.

March 31, 1998 Office Action at page 4.

The Gutniak et al. article, either alone or in combination with the '286 patent and the D'Alessio article, does not render the claimed methods and compositions obvious to one of ordinary skill in the art at the time the invention was made.

The infusion experiments described in Gutniak et al. do not support a conclusion that the use of GLP-1 (7-36) amide for the treatment of people with Type 1 diabetes mellitus (IDDM) would have been obvious at the time the invention was made to one of ordinary skill in the art. Indeed, the authors own conclusions support this, for they concluded only that "GLIP has an antidiabetogenic effect, and it may therefore be useful in the treatment of patients with NIDDM [Type 2 diabetes mellitus]" (Gutniak et al., Abstract). They said nothing about the treatment of other kinds of patients.

Additionally, as stated at page 1, lines 19-22 of the specification, "GLP-1(7-36)amide . . . is a gastrointestinal peptide which potentiates insulin release in response to glycaemia in normal humans." However, in Type 1 diabetes, insulin is deficient or completely lacking. Thus, it would have been completely unexpected that an agent which was believed to be

useful only because of its ability to potentiate insulin release could be useful in the treatment of people with Type 1 diabetes, who do not have the ability to produce sufficient insulin. Stated another way, for those individuals who have lost the ability to secrete insulin, there is no secretory response for GLP-1(7-36) amide to amplify.

The Examiner's statement that, "Since Gutniak et al., teaches that GLP-1(7-36)amide decreases the need for external insulin in Type I diabetics after a meal, it would be obvious to treat Type I diabetics with the peptide," is not correct. Gutniak et al. reported on two types of studies involving IDDM (type 1 diabetic) patients relating to insulin action: (1) Biostator experiments in which patients were connected to a closed-loop insulin-infusion system and received insulin intravenously to keep their blood glucose concentrations normal; and (2) Hyperinsulinemic-normoglycemic-clamp studies, in which blood glucose concentration was kept constant and glucose utilization calculated. The Biostator experiments reportedly indicated that a constant infusion of GLP-1(7-36)amide led to decreased insulin required to maintain a constant plasma glucose concentrations. The glycemic clamp experiments reportedly indicated that a constant infusion of GLP-1(7-36) amide led to an increased glucose infusion rate in order to maintain normoglycemia.

Gutniak et al. concluded that "GLIP stimulates insulin release" and "improves insulin sensitivity." Gutniak et al. at page 1319, Discussion. This does not support a determination that GLP-1 (7-36)amide would have been viewed by one of ordinary skill as per se useful in the treatment of Type I diabetes

mellitus, particularly in light of the fact that people with frank Type 1 diabetes do not produce endogenous insulin -- which is the hallmark of this disease -- because their insulin-producing pancreatic beta cells have been destroyed. Increased insulin sensitivity would not eliminate the need for insulin injections in patients unable to produce insulin. Further, insulin resistance is not a problem in type 1 diabetics as it is in type 2 diabetics (for whom Gutniak et al., in contrast, do propose utility.

One skilled in the art would not glean from the Gutniak et al. article as a whole (including, e.g., the conclusion in the Abstract relating to only Type 2 diabetes) that Type 1 diabetes could be treated by administration of GLP-1 (7-36) amide.

As noted above, Gutniak et al. recognized that the data disclosed did not support the use of GLP-1 (7-36) amide for the treatment of Type I diabetes mellitus (IDDM). For example, they stated in the Abstract only that GLP-1 (7-36) amide "has an antidiabetogenic effect, and it may therefore be useful in the treatment of patients with NIDDM [Type 2 diabetes mellitus]," and then concluded only that:

> A better treatment for patients with NIDDM [Type 2 diabetes mellitus] who do not respond to sulfonylurea therapy would be one that decreases their requirement for insulin and therefore decreased the occurrence of hypoglycemia. Our study demonstrates that at least in the short term, the administration of GLIP decreases postprandial insulin requirements and plasma insulin concentrations <u>in patients with NIDDM</u>. Therefore, the

peptide may have a role in the treatment of some patients with diabetes.

Gutniak et al., at page 1321 (emphasis added). Thus, although Gutniak et al. states that in these laboratory infusion studies GLP-1 (7-36) amide decreased the meal-related insulin requirement in Type 1 diabetes (IDDM) patients under controlled euglycemic conditions, the treatment of Type 1 diabetes is neither disclosed under § 102 or suggested within the meaning of § 103, and is not even mentioned in either their introduction or their conclusion.

The Examiner appears to be relying on only select portions of the Gutniak et al. article in making a rejection, while ignoring other portions of the article which do not support the Examiner's position. This is impermissible under the patent laws. See, e.g., In re Wesslau, 147 USPQ 391,393 (CCPA 1965) ("It is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art.").

Neither the '286 patent nor the D'Alessio article supply what the Gutniak et al. article lacks. The '286 patent relates to Gila Monster polypeptides ("exendins") and pharmaceutical compositions comprising them. The '286 patent provides no data on GLP-1 peptides and contains only brief mention of Gutniak et al. in the background section of the patent. As noted above, the discussion of Gutniak et al. in the '286 patent must be read in light of the entire Gutniak, et al. article and the entire '286 patent. When it is read in this

manner, it is apparent that the '286 patent mischaracterizes Gutniak et al. if read in the manner suggested by the Examiner.

As discussed above, the Gutniak et al. article describes, not the treatment of IDDM patients, but day-long laboratory experiments to evaluate the effects of GLP-1 (7-36) amide in which individuals were hooked to a machine which allowed the continuous infusion of GLP-1 (7-36) amide for over 3 ½ hours into the contralateral antecubital vein at 0.75 pmol per kilogram of body weight per minute, or in clamp studies in which GLP-1 (7-36) amide was constantly infused over four hours at a rate of 0.75 pmol per kilogram per minute. In analyzing their results, Gutniak et al. stated that, "Since GLP-1 (7-36) amide, the naturally occurring form in humans, is released during a meal, and after oral glucose administration and potentiates glucose-induced insulin release, this truncated form of GLP-1 may be an important incretin" (defined in Gutniak et al. as "an endocrine transmitter that is produced in the gastrointestinal tract, is released by food intake (especially of carbohydrates), and stimulates insulin secretion in the presence of plasma peptide concentrations not exceeding those reached after meals"). Thus, they concluded only that GLP-1 (7-36) amide -- referred to as exerting a strong "insulinotrophic" (insulin-releasing) effect -- may have a role in the treatment of "some patients with diabetes," i.e., Type II patients who still retain the ability to secrete endogenous insulin. Accordingly, the statement in the '286 patent that, "[Gutniak et al.] reasoned that since GLIP is the naturally active form found in humans after a meal, this peptide may aid in glucose regulation in IDDM and NIDDM," is not accurate.

Nor is the following conclusion in the '286 patent accurate:

> In patients with IDDM, the GLIP treatment lowered the insulin required by one-half. This glucose-dependent activity is a very desirable characteristic for a therapeutic agent that can be used to treat DM avoiding tile [sic, the] complications of hypoglycemic side effects.

Insulin acts to decrease blood glucose. Thus, increased insulin sensitivity results in an increase in the blood glucose lowering effects (i.e., increased hypoglycemia) activity of insulin. Accordingly, contrary to the conclusion in the '286 patent, an increase in insulin sensitivity would be expected to, if anything, increase - not decrease -- hypoglycemia. This is the opposite of what is stated in the '286 patent.

Nor does the D'Alessio article support the Examiner's assertions. For the reasons set forth above with respect to the Gutniak et al. article and the '286 patent, the D'Alessio article does not suggest the claimed compositions and methods. As noted above, both the entire D'Alessio article and the entire Gutniak et al. article must be considered when examining the statements in the Introduction and Abstract of the D'Alessio article to which the Examiner refers. For example, after the language quoted by the Examiner, the D'Alessio article points out some of the deficiencies of the Gutniak et al. article:

> It has recently been reported that infusions of GLP-1 into diabetic subjects decreased the insulin dosage required to maintain euglycemia. Furthermore, type I diabetic subjects treated with GLP-1 during one step euglycemic, hyperinsulinemic clamps had 10-15% higher rates of glucose than during control studies, thereby suggesting that GLP-1 may promote glucose uptake in addition to augmenting insulin

> release. However, it cannot be determined from these data whether GLP-1 exerts an effect on insulin sensitivity, or if it promotes insulin-independent glucose disposition. Furthermore, because glucose disposal rates were studied only in diabetic subjects, it is not known whether their augmentation by GLP-1 occurs in healthy people, and this might comprise a physiologic response of the peptide.

D'Alessio at page 2263, column 2, first full paragraph (emphasis added).

Thus, it is clear that when each of the items cited by the Examiner is considered as a whole, the Gutniak et al. article, either alone or in combination with the '286 patent or the D'Alessio article, neither discloses nor suggests the presently claimed compositions and methods.

The Examiner states at page 4 of the March 31, 1998 Office Action:

> Applicant is notified that as of the current search in the prior art claims 20-22 and 28-30 are only objected to because they depend upon rejected claims.

In view of this statement with respect to claims 20-22 and 28-30, which relate to subcutaneous administration, it is submitted that the current claims, which also specify modes of administration, will be similarly viewed by the Examiner.

Applicant thus requests that the section 103 rejection of claims 15-19, 23-27, 33 and 36 be reconsidered and withdrawn.

CONCLUSION

For the reasons set forth above, applicant believes that the pending claims are in condition for allowance and seeks early Notice thereof. If any issues or questions arise, the Examiner is encouraged to telephone the undersigned so they may be resolved promptly.

Respectfully submitted,

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By _____

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